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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	GUY A. ROULEAU et al.
Serial No.:	09/508,821
Filed:	May 26, 2000
Group Art Unit	1655
Examiner:	J. A. GOLDBERG
Title:	**POLYMORPHIC CAG REPEAT-CONTAINING GENE AND USES THEREOF**

SUPPLEMENTAL AMENDMENT

Commissioner for Patents
Washington, D.C. 20231
U.S.A.

Dear Sir:

This Supplemental Amendment is in response to a January 28, 2002 Official Action. This Supplemental Amendment is aimed at correcting deficiencies in the Sequence Listing and at amending the claims as requested by the Examiner so that they also satisfy the Sequence Listing Rules. Response to the Office Action is due on June 28, 2002, with a four-month (4) extension of time. The Applicants submit concurrently a Petition for Extension of Time for four months, to and including June 28, 2002, accompanied by the required fee.

IN THE SPECIFICATION:

Please amend lines 16-17 at page 9 so that they now read:

E1

followed by CAA ($CAG_{9-13}CAA$), (SEQ ID NOs:19-23) with the exception of the 13Q allele which is $CAGCAACAG_{10}CAA$ (SEQ ID NO:18).

IN THE CLAIMS:

Please amend the claims as follows:

E2

1. (Twice amended) An isolated human hGT1 gene comprising a transcribed polymorphic CAG repeat having the sequence $(CAR)_2(CAG)_nCAA$, wherein R is A or G and n is from 7 to 12, as set forth in SEQ ID NOs:12-17, wherein allelic variants of said CAG repeat are associated with a disorder selected from the group consisting of psychiatric diseases, schizophrenia, affective disorders, neurodevelopmental brain diseases and phenotypic variability with respect to long term response to neuroleptic medication, and wherein n being equal to 11 (SEQ ID NO:16) is the most common allele of the hGT1 gene.

2. The gene of claim 1, wherein said affective disorder is manic depression.

E3

3. (Twice amended) A method for evaluating the severity of schizophrenia of a patient, which comprises the steps of:

a) obtaining a nucleic acid sample of said patient; and

b) determining allelic variants of said CAG repeat of the gene of claim 1,

wherein allelic variants shorter than allele 0, which corresponds to n=11 (SEQ ID NO:16), are indicative of less severe schizophrenia in the patient.

4. A method for the identification of the response of a patient to neuroleptic medication, which comprises the steps of:

a) obtaining a nucleic acid sample of said patient; and

b) determining allelic variants of said CAG repeat of the gene of claim 1,

wherein allelic variants shorter than allele 0, which corresponds to n=11, are indicative of a neuroleptic response by said patient.

E4

5. (Twice amended) The method of claim 4, wherein said shorter allelic variants have a n equal to 8, 9 or 10 as set forth in SEQ ID NOs:13, 14 or 15.

9. A method of categorizing a psychiatric patient according to its genotype in order to maximize its response to treatment to at least one neuroleptic drug, which comprises the steps of:

a) obtaining a nucleic acid sample of said patient; and

b) determining allelic variants of said CAG repeat of the gene of claim 1,

wherein a patient is categorized with respect to his allelic variants, and wherein allelic variants shorter than allele 0, which corresponds to n=11, are indicative of a neuroleptic response of said patient.

10. A method of identifying a patient which is responsive to a neuroleptic medication which comprises:

a) obtaining a sample from said patient; and

b) determining allelic variants of said CAG repeat of the gene of claim 1, wherein allelic variants shorter than allele 0, which corresponds to n=11, identify said patient as a neuroleptic responder.

ES

11. (Amended) The method of claim 10, wherein said sample is a nucleic acid sample and wherein shorter allelic variants have a n equal to 8, 9 or 10, as set forth in SEQ ID NO:13, 14 or 15.

E6

13. (Amended) The human gene of claim 1, wherein n is selected from the group consisting of 7, 8, 9, 10 and 12, as set forth in SEQ ID NOs:12, 13, 14, 15 and 17, and wherein said allelic variant is associated with schizophrenia.

14. (Amended) The human gene of claim 13, wherein n is selected from:

a) n is 7 to 10, as set forth in SEQ ID NOs:12 to 15, wherein said allelic variant is associated with a neuroleptic medication-responsive status of a schizophrenic patient, and

b) n is equal to 12, as set forth in SEQ ID NO:17, wherein said allelic variant is associated with a poor responsive status of a schizophrenic patient to neuroleptic medication.

15. The human gene of claim 1, wherein n is equal to 11, which comprises the sequence as set forth in SEQ ID NO:2.

16. The human gene of claim 15 comprising the sequence as set forth in SEQ ID NO:5.

17. An isolated nucleic acid sequence comprising the sequence as set forth in SEQ ID NO:2.

18. The isolated nucleic acid sequence of claim 17 comprising the sequence as set forth in SEQ ID NO:5.

19. An isolated nucleic acid sequence comprising a sequence encoding the amino acid sequence as set forth in SEQ ID NO:6.

20. A vector which expresses the isolated nucleic acid sequence of claim 17.

21. A vector which expresses the isolated nucleic acid sequence of claim 18.

22. A vector which expresses the gene of claim 1.

23. A cell harboring the vector of claim 20.

24. A cell harboring the vector of claim 21.

25. A cell harboring the vector of claim 22.

REMARKS

Claims 1, 3-5, 9-11, and 13-25 are still in the case.

Applicants provide concurrently herewith a second substitute Sequence Listing with computer-readable copy and a statement under 35 CFR ∋ 1.821(f). This second substitute Sequence Listing is provided herewith to insert sequences having more than 10 nucleotides, such as those noted by the Examiner at Section "A)" of the Office Action, as well as those found in the claims. Accordingly, the specification and claims have been amended so as to refer to the sequences by their respective SEQ ID NOs.

At paragraph "B)", the Examiner objects to the use of the letter "U" instead of "R". Accordingly, claim 1 has been amended so that it now replaces "U" by "R".

In Paragraph "C)" of the Office Action, the Examiner is of the opinion that SEQ ID NO:5 is indeed supported by the original disclosure. She believes however that

> "Based upon the text of the specification, it appears as though there are 490 bps plus 19 bps prior to the ORF, such that there are 509 bps prior to the translation start site. The amendment which has added the protein sequence appears to being at nucleotide position 490. Therefore, there is neither a 490 bps intron preceding the ORF nor the 490 bps intron and 19 bps of the 5'UTR. Thus, insertion of a start site at position 490 does not appear to be supported by the original disclosure". [emphasis added]

Firstly, the Applicants apologize for the confusion surrounding the characterization of the open-reading frame encoded by SEQ ID NO:5. Indeed, as observed by the Examiner, unfortunately, the initiator AUG is not bold in Figure 4A. A clerical error can be blamed for this fact. Applicants submit herewith a copy of the sequence provided by the inventor Guy Rouleau which was used initially to prepare the priority application, and obtained from the firm who prepared and filed both the priority and PCT applications from which the instant application emanates (Appendix A), showing that, as stated, the ATG at 490 is bold and is thus the initiator.

The initiator ATG starting at position 490 in SEQ ID NO:5 is preceded by a total of 490 bps including a 19 bps exon of 5'UTR. Clearly, it appears that a clerical error in the enunciation of the characterization of the 490 bps upstream of the initiator AUG in the specification was not corrected by the inventors or the previous firm who drafted and filed this case (the same applies to the bold characters in Figure 4). Figure 4A indeed shows 19 bps in uppercase (i.e. exon sequences; see the Figure legend of Fig. 4A-4E at page 7), consistent with the fact that the initiator ATG is preceded by a 19 bp 5'UTR. The Applicants respectfully submit, in addition, that, in view of (1) Appendix A; and (2) the fact that a very long open-reading frame of 1755 amino acids is encoded starting at the ATG at position 490 in SEQ ID NO:5, it should be clear to the Examiner that the translation of the nucleic acid sequence in SEQ ID NO:5 is not new matter and was intrinsic to the sequence as originally filed and as described starting at page 8, albeit with some minor mistakes. In support of this contention, the Examiner is respectfully referred to the amino acid sequence taken from SEQ ID NO:5 and especially position 278 to 291 (in bold here)

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tcg ggc cgc ctc agc tat gac cag cag cag cag cag cag cag cag cag 1347
Ser Gly Arg Leu Ser Tyr Asp Gln Gln Gln Gln Gln Gln Gln Gln Gln
                275                 280                 285

cag cag cag cag caa gcc ctt cag agc cgg cac cat gcc cag gaa acc 1395
Gln Gln Gln Gln Gln Ala Leu Gln Ser Arg His His Ala Gln Glu Thr
            290                 295                 300
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which provides the sequence of the most common allele in hGT1 as defined in SEQ ID NO:16 and as in claim 1 "wherein n being equal to 11 is the most common allele of the hGT1 gene". The Examiner will note that this polymorphic CAG repeat is in frame with the open-reading frame starting at position 490, thereby clearly demonstrating that the ORF initiating at 490 is supported by the disclosure as filed.

In view of the above and foregoing, the Applicants respectfully submit that the translated open-reading frame present in the nucleic acid sequence of SEQ ID NO:5 is not new matter and is, as stated previously, intrinsic to the nucleic acid sequence.

With respect to the numerous termination sites "TGA", the Applicants respectfully disagree with the fact that this is indicative that the region is not a coding region. However, it stands to reason that SEQ ID NO:5, as translated presently, is truncated at amino acid 1755 and is thus missing a number of C-terminal amino acids. Nevertheless, the Applicants respectfully submit that the arguments provided above clearly show that SEQ ID NO:5 indeed contains the coding region claimed.

Applicants further advise that a +1 frameshift starting at position 1755 of SEQ ID NO:5 enables the ORF to continue until position 6022. The fact that no termination codon is encountered would be in agreement that "we are still missing the sequences coding for the 12 amino acids (36 bp)". As of the filing of this response, the discrepancy in SEQ ID NO:5 and the statement that "TG1 includes a 5535 bps open-reading frame (ORF) of 5535 bps without interruption" is not understood.

Taken together, it is respectfully submitted that the ORF as defined in SEQ ID NO:6 is supported by the disclosure as filed.

In the event that there are any questions concerning the amendment or application in general, the Examiner is respectfully urged to telephone the undersigned so that the prosecution of the application may be expedited.

Authorization is hereby given to charge deposit account no. 05-1323 for any deficiency in fees or for credit of any overpayment in connection with this response.

Respectfully submitted,

June 28, 2002

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